Dihydroergotamine (BREKIYA) for Subcutaneous Injection
Abbreviated National Drug Monograph

February 2026

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

This abbreviated monograph is intended to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating Dihydroergotamine subcutaneous injection (BREKIYA) and its VA National Formulary status; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA

FDA PRESCRIBING INFORMATION[1]

Description / MOA	Dihydroergotamine (DHE) is an agonist at 5-HT1B,1D receptors on cranial blood vessels, resulting in vasoconstriction. Activation of 5-HT1D receptors also inhibits release of pro-inflammatory neuropeptides (calcitonin gene-related peptide, CGRP) on sensory nerve endings of the trigeminal system.
Indication Under Review	Acute treatment of migraine with or without aura and the acute treatment of cluster headaches in adults.
Dosage Regimen	1 mg subcutaneously (subQ) at first sign of migraine. Additional 1 mg doses may be administered at 1-hour intervals with a maximum of 3 mg in 24 hours (no more than 6 mg total in a week).
Dosage Forms Under Review	1 mg/mL dihydroergotamine mesylate as a 1 mL single-dose autoinjector.

EFFICACY CONSIDERATIONS

No new efficacy trials were required for FDA approval of BREKIYA via the abbreviated approval pathway for a new dosage form. Approval was based on the results of previous evidence with DHE which are briefly summarized below.

Trial	**Winner et al. 1996, SubQ DHE versus subQ sumatriptan for the treatment of acute migraine[2]**
Design	Double-blind, randomized trial with parallel treatment arms n=310 (152 received DHE and 158 received sumatriptan)
Results	Headache relief was defined as a rating of "none" or "mild" on a headache pain scale. Headache recurrence was only counted if the patient had experienced headache relief at 3 hours, but the pain intensity subsequently increased. SubQ DHE had a significantly lower rate of headache relief at one hour, but a significantly higher rate of relief at 24 hours. SubQ DHE also had a significantly lower rate of recurrence compared to subQ sumatriptan.

Outcome	SubQ DHE	SubQ Sumatriptan
Headache relief at 1 hour	56.6%*	78%
Headache relief at 3 hours	86%	90%
Headache relief at 24 hours	89.7%*	76.7%
Headache recurrence within 24 hours	17.7%*	45%
*statistically significant treatment difference p<0.05		

Trial	**Mather et a. 1991, Cluster Headache treatment with intravenous (IV) DHE[3]**
Design	Retrospective review of 54 people with Cluster Headache treated with repetitive IV DHE.
Results	15.6% were headache free after the first dose. 81.4% were headache-free by the second day. All patients became headache-free by 6 days of treatment with IV DHE.

SAFETY CONSIDERATIONS[1]

Boxed Warnings	Co-administration with strong CYP3A4 inhibitors has been associated with serious and/or life-threatening peripheral ischemia.
Contraindications	Ischemic heart disease/coronary artery vasospasm, uncontrolled hypertension, peripheral artery disease, sepsis, following vascular surgery, severe hepatic or renal impairment, latex allergy, use of serotonin agonists or ergot-type medications within 24 hours, and concomitant use of peripheral and central vasoconstrictors.
Other Warnings	Cerebrovascular hemorrhage, subarachnoid hemorrhage, stroke, increased blood pressure, medication overuse headache, pleural and retroperitoneal fibrosis.
Top 5 AEs	Nausea, vomiting, diarrhea, dizziness, drowsiness
Drug Interactions	Beta blockers and nicotine may worsen or provoke vasoconstriction. Use with selective serotonin reuptake inhibitors have been reported rarely to produce weakness, hyperreflexia, and incoordination.
Pregnancy	DHE may cause preterm labor. Use is not recommended in pregnancy.
Lactation	Breastfeeding should be avoided during treatment and for 3 days after the last dose. Ergotamine is excreted in breastmilk and reports of vomiting diarrhea, weak pulse, and unstable blood pressure have been reported in infants.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY: injection and nasal drugs for migraine and/or cluster headache acute treatment[4-7]

DRUG	VANF	CFU	Migraine Indication	Cluster Headache Indication	Migraine Guidelines	Cluster Headache Guideline
DHE inj	Yes	No	Yes	Yes	2024 IHS: Consider if all other recommended agents with better safety profile have failed 2023 VA/DOD: NR 2015 AHS: Probably effective	2023 VA/DoD: NR 2016 AHS: NR
DHE nasal	No	No (generic)	Yes	No	2024 IHS: Consider if all other recommended agents with better safety profile have failed 2023 VA/DOD: NR 2015 AHS: Established as effective	2023 VA/DoD: NR 2016 AHS: Insufficient evidence
Sumatriptan inj	Yes	No	Yes	Yes	2024 IHS: Suggested in non-response to NSAID or analgesic 2023 VA/DOD: Strong for 2015 AHS: Established as effective	2023 VA/DoD: Weak for 2016 AHS: Established as effective
Sumatriptan nasal	Yes (generic, TOSYMRA) No (ONZETRA XSAIL)	No	Yes	No	2024 IHS: Suggested in non-response to NSAID or analgesic 2023 VA/DOD: NR 2015 AHS: Established as effective	2023 VA/DoD: NR 2016 AHS: Probably effective
Zolmitriptan nasal	Yes	No	Yes	No	2024 IHS: Suggested in non-response to NSAID or analgesic 2023 VA/DOD: Strong for 2015 AHS: Established as effective	2023 VA/DoD: Weak for 2016 AHS: Established as effective
Zavegepant nasal	No	Yes	Yes	No	2024 IHS: Suggested in non-response or contraindication to triptan alone and triptan+NSAID 2023 VA/DOD: NR 2015 AHS: NR	2023 VA/DoD: NR 2016 AHS: NR

AAN: American Academy of Neurology; AHS: American Headache Society; IHS: International Headache Society; NR: no recommendation

POTENTIAL PLACE IN THERAPY

1. BREKIYA is a new delivery device (prefilled autoinjector) for subcutaneous administration of dihydroergotamine. It is FDA-approved for the acute treatment of migraine and cluster headache based on previous studies for dihydroergotamine for injection (DHE inj.).
2. For migraine, DHE inj. has a slower onset of efficacy compared to triptans, though a better prevention of recurrence within 24 hours.[2] Most recent guidelines for migraine prefer triptans and gepants over DHE largely due to side effect profile.[4] DHE nasal has a stronger recommendation ("established as effective") than DHE inj. ("probably effective") for acute migraine treatment in the 2015 AHS guideline.[6]
3. For cluster headache, there are fewer options for acute treatment as a fast-acting acute therapy is required. DHE inj. and sumatriptan inj. are FDA-approved and there is evidence supporting nasal triptans for acute cluster headache treatment.[5,7] It should be noted that recent guidelines prefer triptans to DHE for acute cluster headache treatment.
4. Generic DHE inj. is packaged in glass ampules. The new delivery device offers a much easier and safer method for self-administered injection of DHE as there is no need to break glass ampules, use filter needles, and switch the needle for administration.
5. When considering the overall evidence, DHE inj. is not recommended as a first-line treatment for acute migraine or cluster headache. However, it may offer an acute treatment option for people with migraine or cluster headache who have experienced inefficacy, intolerance, or have a contraindication to preferred evidence-based alternatives. In the niche clinical situation where a patient requires DHE inj. for outpatient self-administration, the autoinjector may be preferred over glass ampules.

Original: Feb 2026. Contact person: N. Antonovich, PharmD, BCPS, National Program Manager, VA Pharmacy Benefits Management Services – Formulary Management (12PBM)

References

1. BREKIYA (diphenhydramine) injection [prescribing information online]. Bridgewater, NJ: Amneal. July 2025.
2. Winner P, Ricalde O, Le Force B, et al. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol. 1996;53:180-184.
3. Mather PJ, Silberstein SD, Schulman EA, McFadden Hopkins M. The treatment of cluster headache with repetitive intravenous dihydroergotamine. Headache 31:525-532, 1991.
4. Puledda F, Sacco S, Diener H-C, et al. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. Cephalgia. 2024, 44(8): 1-45.
5. VA/DoD Clinical Practice Guideline. (2023). Management of Headache Work Group. Washington, DC: U.S. Government Printing Office.
6. Marmura MJ, Silberstein SD, Schwedt TJ. American Headache Society evidence assessment. Headache. 2015; 55:3-20.
7. Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of cluster headache: the American Headache Society Evidence-Based Guidelines. Headache. 2016; 56:1093-1106.